Available online at www.worldscientificnews.com

World Scientific News

An International Scientific Journal

WSN 120(2) (2019) 286-290 EISSN 2392-2192

SHORT COMMUNICATION

Endothelial progenitor cell dysfunction: is it best fitted for risk stratification in pulmonary disease?

Alexander E. Berezin[1,*], Alexander A. Berezin[2]

[1]Internal Medicine Department, State Medical University of Zaporozhye,
26, Mayakovsky av., Zaporozhye, Ukraine

[2]Internal Medicine Department, Medical Academy of Postgraduate Education, Zaporozhye, Ukraine

*E-mail address: aeberezin@gmail.com , dr_berezin@mail.ru

*Phone: +380612894585

ABSTRACT

Endothelial progenitor cell (EPC) dysfunction is defined as weak function and lowered number of endothelial precursors with pro-angiogenic phenotypes that are imbedded in vascular integrity maintenance, angiogenesis, and vascular reparation. There is large body of evidence that deficiency of EPC number in peripheral blood is considered as a marker of endothelial dysfunction, which is established risk factor and player in pathogenesis of cardiovascular disease. Moreover, recent clinical studies have shown that circulating EPCs had demonstrated vascular protection in several vascular diseases including pulmonary hypertension. However, the role of EPCs in pathogenesis chronic obstructive pulmonary disease bronchial asthma, emphysema appeared to be uncertain. The short communication is dedicated the controversies in abilities of EPCs to have tissue protective and play a pivotal role in nature evolution of pulmonary disease.

***Keywords*:** pulmonary disease, cardiovascular risk, endothelial dysfunction, endothelial precursors, prediction, prognosis

(Received 03 February 2019; Accepted 13 February 2019; Date of Publication 14 February 2019)

1. INTRODUCTION

Endothelial progenitor cells (EPCs) are defined as various populations of primitive CD34+ endothelial precursors with different origin that additionally express CD31, CD133, CD144 and VEGFR2 antigens [1]. Although previous investigations, which had seized molecular characteristics of EPCs, have sufficiently been distinguished in hierarchy, colony-forming and proliferation capacities, as well as immune phenotypes [2, 3], the most specific property of these cells remained an ability to be a source for renewal of mature endothelial cells [4]. Thus, EPCs are determined as a component of endogenous vascular repair system that supports vascular integrity, endothelial function, angiogenesis, neovascularization and reparation [5].

There is a large of body evidence that decreased number and / or weak function of EPCs known as EPC dysfunction frequently proceeded to developing cardiovascular (CV) disease and / or CV events and also accompanied CV risk factors [6-8]. Indeed, declined number of circulating EPCs was associated with CV complications, but restoring of a pole of angiopoetic endothelial precursors was related to an attenuation of vascular function, decreasing of a risk of CV events and improving of clinical outcomes [9, 10]. It has been suggesting that EPCs were not just able to produce wild range of spectrum of angiopoetic factors contributing in the angiogenesis and vascularization (hormones, microRNAs, growth factors, active peptides and molecules), but they are directly imbedded in the differentiation into mature endothelial cells and smooth muscle cells of vascular wall supporting vascular integrity and function [11].

The regulation of autocrine EPC function is performed through several signal systems (Akt, nuclear factor-kappa B; STAT, and Notch signaling) and epigenetically via target genes (hey1, hes1, cdkn1c and il33) that mediate an activity of intracellular signal systems [12]. Key triggers for EPC activity were pro-inflammatory cytokines (tumor necrosis factor-alpha, interleukin-6), growth factors (vascular endothelial growth factor, transforming growth factor-beta, hypoxia inducible factor-1), hormones (angiotensin-II, renin, and endothelin-1), and oxidative stress components (oxidized lipids) [13].

EPCs are implicated in the pathogenesis of numerous respiratory diseases, including chronic obstructive pulmonary disease (COPD) and emphysema and correspond to CV risk in the diseases [11, 14]. It is well known that mobbing and differentiation of EPCs mediate airway wall neovascularisation, which is a prominent feature of COPD, is associated with reticular basement membrane thickening and airway obstruction [15]. Additionally, sub-epithelial vascularization in COPD may be an important remodeling event for airway narrowing and airflow obstruction. On the other hand, deficiency of EPCs corresponded to endothelial dysfunction, which is core element on pathogenesis of pulmonary hypertension in COPD and emphysema patients. In this context, EPCs may play controversial role in COPD nature evolution. The results of the Multi-Ethnic Study of Atherosclerosis COPD Study recruited smokers with age from 50 years to 79 years without clinical CV disease revealed that populations of pro-angiogenic EPCs with immune phenotypes CD34+VEGFR+ and CD34+VEGFR+CD133+ cells were significantly reduced in COPD and emphysema patients in comparison with healthy volunteers.

Moreover, number of circulating CD34+VEGFR+CD133+ EPCs was associated inversely to severity of emphysema [16], was not related to COPD severity [17]. Noted there was not significant difference between number of circulating EPCs in smokers and nonsmokers [18]. Additionally, number of EPCs in peripheral blood predicted cardiac dysfunction due to

COPD and strong associated with morbidity in patients with acute exacerbation of COPD [19]. There is point of view that chronic inflammation that is suitable for COPD does not impact only on bronchial wall and lung parenchyma, buy yet it potentially exists as systemic phenomenon, which reduces vasodilatation capacity, enhanced blood coagulation, and increased platelet activation resulting in higher risk of CV complications [20, 21].

Thus, EPCs plays positive role in supporting vascular integrity and function, but they influence negatively on bronchial remodeling. On contrary, there is evidence that EPCs are able to attenuate developing pulmonary emphysema and improve of lung function by alleviating inflammatory infiltration in alveoli, decelerating apoptosis of alveolocytes, inhibiting proteolytic enzyme activity, and improving antioxidant defense [22, 23]. Finally, these findings require to be investigated in details in large clinical trials in the future.

2. CONSLUSIONS

In conclusion, EPCs may play a duel role in the pathogenesis of pulmonary disease. On the one hand, they contribute vascular repair, support endothelial function and maintain lung homeostasis. On the other hand, angiogenesis in sub-intima of bronchial wall provide reticular basement membrane thickening and lead to airway obstruction. Both abilities of EPC subsets expressed angiogenesis-related molecules require to be accurate identified and compared each other in clinical studies affecting several populations of the patients with established pulmonary diseases.

References

[1] Patel J, Donovan P, Khosrotehrani K. Concise Review: Functional Definition of Endothelial Progenitor Cells: A Molecular Perspective. *Stem Cells Transl Med.* 2016; 5(10): 1302-1306

[2] Masuda H, Alev C, Akimaru H, et al. Methodological development of a clonogenic assay to determine endothelial progenitor cell potential. *Circ Res.* 2011; 109: 20–37

[3] Patel J, Seppanen E, Chong MS, et al. Prospective surface marker-based isolation and expansion of fetal endothelial colony-forming cells from human term placenta. *Stem Cells Translational Medicine* 2013; 2: 839–847

[4] He S, Nakada D, Morrison SJ. Mechanisms of stem cell self-renewal. *Annu Rev Cell Dev Biol.* 2009; 25: 377–406

[5] Berezin A. The endothelial progenitor cell dysfunction in hypertension: the diagnostic and predictive values. *Vessel Plus.* 2018; 2: 22. doi:10.20517/2574-1209.2018.23

[6] Keighron C, Lyons CJ, Creane M, O'Brien T, Liew A. Recent Advances in Endothelial Progenitor Cells Toward Their Use in Clinical Translation. *Front Med (Lausanne).* 2018; 5: 354. doi:10.3389/fmed.2018.00354

[7] Berezin A, Kremzer A, Berezina T, Martovitskaya Y, Gromenko E. Data regarding association between serum osteoprotegerin level, numerous of circulating endothelial-

derived and mononuclear-derived progenitor cells in patients with metabolic syndrome. *Data in Brief.* 2016; 8: 717-722. doi:10.1016/j.dib.2016.06.015

[8] Berezin A. Up-to-date clinical approaches of biomarkers' use in heart failure. *Biomed Res Ther.* 2017; 4(6): 1341-1370 doi:10.15419/bmrat.v4i06.178

[9] O'Neill CL, McLoughlin KJ, Chambers SEJ, Guduric-Fuchs J, Stitt AW, Medina RJ. The Vasoreparative Potential of Endothelial Colony Forming Cells: A Journey Through Pre-clinical Studies. *Front Med (Lausanne)* 2018; 5: 273. doi:10.3389/fmed.2018.00273

[10] Berezin A. Progenitor endothelial cell dysfunction in heart failure: clinical implication and therapeutic target? *Translational Medicine* 2016; 6(3): 176-177. doi:10.4172/2161-1025.1000176

[11] Guerra G, Perrotta F, Testa G. Circulating Endothelial Progenitor Cells Biology and Regenerative Medicine in Pulmonary Vascular Diseases. *Curr Pharm Biotechnol.* 2018; 19(9): 700-707. doi:10.2174/1389201019666181017161752

[12] Berezin A. Epigenetically Modified Endothelial Progenitor Cells in Heart Failure. *J Clin Epigenet.* 2016; 2(2): 21-23

[13] Rafii S, Butler JM, Ding BS. Angiocrine functions of organ-specific endothelial cells. *Nature* 2016; 529: 316–325

[14] Coppolino I, Ruggeri P, Nucera F, Cannavò MF, Adcock I, Girbino G, et al. Role of Stem Cells in the Pathogenesis of Chronic Obstructive Pulmonary Disease and Pulmonary Emphysema. *COPD* 2018; 15(5): 536-556. doi:10.1080/15412555.2018.1536116

[15] Salter B, Sehmi R. The role of bone marrow-derived endothelial progenitor cells and angiogenic responses in chronic obstructive pulmonary disease. *J Thorac Dis*. 2017; 9(7): 2168-2177. doi: 10.21037/jtd.2017.07.56

[16] Doyle MF, Tracy RP, Parikh MA, Hoffman EA, Shimbo D, Austin JH, et al. Endothelial progenitor cells in chronic obstructive pulmonary disease and emphysema. *PLoS One* 2017; 12(3): e0173446. doi:10.1371/journal.pone.0173446

[17] Palange P, Testa U, Huertas A, Calabro L, Antonucci R, Petrucci E et al. Circulating haemopoietic and endothelial progenitor cells are decreased in COPD. *Eur Respir J.* 2006; 27: 529–541

[18] García-Lucio J, Peinado VI, de Jover L, Del Pozo R, Blanco I, Bonjoch C, et al. Imbalance between endothelial damage and repair capacity in chronic obstructive pulmonary disease. *PLoS One* 2018; 13(4): e0195724. doi:10.1371/journal.pone.0195724

[19] Liu X, Liu Y, Huang X, Lin G, Xie C. Endothelial progenitor cell dysfunction in acute exacerbation of chronic obstructive pulmonary disease. *Mol Med Rep.* 2017; 16(4): 5294-5302. doi:10.3892/mmr.2017.7260

[20] Malerba M, Nardin M, Radaeli A, Montuschi P, Carpagnano GE, Clini E. The potential role of endothelial dysfunction and platelet activation in the development of thrombotic risk in COPD patients. *Expert Rev Hematol.* 2017; 10(9): 821-832. doi:10.1080/17474086.2017.1353416..

[21] Berezin A. The Role of Progenitor Endothelial Cell Dysfunction in Arterial Hypertension. *Biological Markers and Guided Therapy* 2018; 5(1): 31-36 doi:10.12988/bmgt.2018.845

[22] Shi Z, Chen Y, Cao J, Zeng H, Yang Y, Chen P, et al. Intratracheal transplantation of endothelial progenitor cells attenuates smoking-induced COPD in mice. *Int J Chron Obstruct Pulmon Dis.* 2017; 12: 947-960. doi:10.2147/COPD.S110781

[23] Salter BM, Manzoor F, Beaudin S, Kjarsgaard M, Nair P, Gauvreau GM, et al. Dysregulation of Vascular Endothelial Progenitor Cells Lung-Homing in Subjects with COPD. *Can Respir J*. 2016; 2016: 1472823. doi:10.1155/2016/1472823